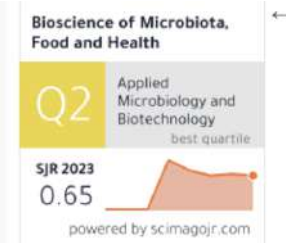
CORRESPONDENCE PAPER

TITLE : Intermittent fasting modulates human gut microbiota diversity in a phenotype-dependent manner: a systematic review

JOURNAL : Bioscience of Microbiota, Food and Health

STATUS : Q2



No	Activity	Date	Page
1	Submit to the journal "Bioscience of Microbiota, Food and Health"	29-12-2023	2-4
2	First revision : with major revision	25-2-2024	5-6
3	Submit first revision	11-3-2024	7-8
4	Second revision : with minor revision	23-3-2024	9-10
5	Submit second revision	24-3-2024	11-12
6	Paper accepted	11-4-2024	13
7	Editorial revision after accepted	18-4-2024	14-34
8	Final data submitted	21-4-2024	35

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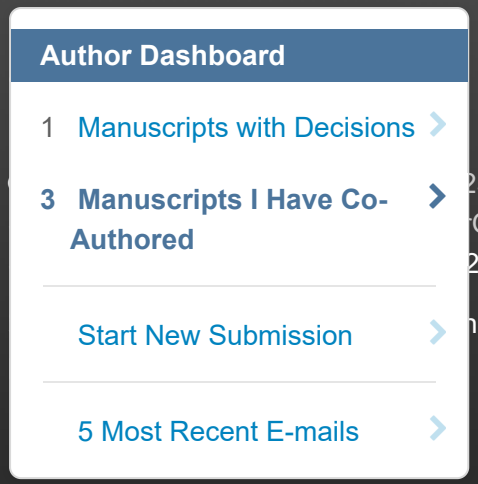
STATUS	ID	TITLE	CREATED	SUBMITTED
Contact Journal ADM: Editorial, Office • Accept (11-Apr-2024) *Archiving completed on 22-Jun-2024*	BMFH-2023-111.R2	Intermittent Fasting Modulates Human Gut Microbiota Diversity in a Phenotype-dependent Manner: A Systematic Review *Files Archived* Submitting Author: Pramono, Adriyan	24-Mar-2024	24-Mar-2024
Contact Journal ADM: Editorial, Office • Minor Revision (23-Mar-2024)	BMFH-2023-111.R1	Intermittent Fasting Modulates the Human Gut Microbiota Diversity in Phenotype Dependent Manner: A Systematic Review *Files Archived*	11-Mar-2024	11-Mar-2024

STATUS	ID	TITLE	CREATED	SUBMITTED
• a revision has been submitted *Archiving completed on 22-Jun-2024*		Submitting Author: Pramono, Adriyan		
Contact Journal ADM: Editorial, Office • Major Revision (25-Feb-2024) • a revision has been submitted *Archiving completed on 22-Jun-2024*	BMFH-2023-111	Intermittent Fasting Modulates the Human Gut Microbiota Diversity in Phenotype Dependent Manner: A Systematic Review *Files Archived* Submitting Author: Pramono, Adriyan	22-Dec-2023	29-Dec-2023



Mail FK UNDIP

Adriyan Pramono <adriyanpramono@fk.undip.ac.id>

Bioscience of Microbiota, Food and Health - Decision on Manuscript ID BMFH-2023-111

1 pesan

Bioscience of Microbiota, Food and Health <onbehalfof@manuscriptcentral.com> 25 Februari 2024 pukul 15.52

Balas Ke: skamiya@ks.kyorin-u.ac.jp
Kepada: adriyanpramono@fk.undip.ac.id

25-Feb-2024

Dear Dr. Pramono:

Manuscript ID BMFH-2023-111 entitled "Intermittent Fasting Modulates the Human Gut Microbiota Diversity in Phenotype Dependent Manner: A Systematic Review" which you submitted to the Bioscience of Microbiota, Food and Health, has been reviewed. The comments of the reviewer(s) are included at the bottom of this letter.

The manuscript has been evaluated by an expert reviewer. The authors are requested to revise it according to the comments from the reviewer.

The reviewer(s) have recommended publication, but also suggest some revisions to your manuscript. Therefore, I invite you to respond to the reviewer(s)' comments and revise your manuscript.

To revise your manuscript, log into https://mc.manuscriptcentral.com/bmfh and enter your Author Dashboard, where you will find your manuscript title listed in "Manuscripts with Decisions." Click on "Create a Revision." Your manuscript number has been appended to denote a revision.

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Please also highlight the changes to your manuscript within the document by using the track changes mode in MS Word or by using bold or colored text.

Once the revised manuscript is prepared, you can upload it and submit it through your Author Center.

When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) in the space provided. You can use this space to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Because we are trying to facilitate timely publication of manuscripts submitted to the Bioscience of Microbiota, Food and Health, your revised manuscript should be uploaded as soon as possible. If it is not possible for you to submit your revision in a reasonable amount of time, we may have to consider your paper as a new submission.

Once again, thank you for submitting your manuscript to the Bioscience of Microbiota, Food and Health and I look forward to receiving your revision.

Sincerely,
Dr. Shigeru Kamiya
Editor in Chief, Bioscience of Microbiota, Food and Health
skamiya@ks.kyorin-u.ac.jp

[Editor's Comments]
Editor
Comments to the Author:
The manuscript has been reviewed by an expert referee. The authors are requested to revise it according to the comments from the referee.

[Reviewer(s)' Comments]
Reviewer: 1

Comments to the Author

The manuscript reviews a clinical importance of intermittent fasting (IF) and its association with human gut microbiota by citing many recent publications. The protocol for the analysis is well designed and the results are well presented. As the manuscript is interesting for better understanding of the efficacy of IF and its effects on microbiota, it is worth reporting in the journal. However, the following points need to be considered.

1.We do not accept “Graphic Abstract”. Therefore, if the figure is necessary, the authors need to add it as Figure 2 in the text.
2. line 76: spp (italic type) ---- spp (roman type)
3. line 114: BMI ---- body mass index (BMI)
4. lines 115, 136: intermittent fasting ---- IF
5. line 167: Full spelling of DASH needs to be written.
6. line 187: Buchinger --- Mesnage et al. Ramadan ---- Ozkull et al.
7. line 200: Ruminococcaceae ----- Ruminococcaceae (27)
8. line 202: Akkermansia (A. muciniphila) ---- Akkermansia muciniphila
9. line 202: B. fragilis ---- Bacteroides fragilis
10. line 204: findings ---- findings (33)
11. lines 206, 217, 247, 344, 392, 415-416: Faecalibacterium prausnitzii --- F. prausnitzii
12. lines 217, 321, 391: Butyricicoccus pullicaecorum ---- B. pullicaecorum
13. lines 218, 344, 396, 400 : Akkermansia muciniphila ---- A. muciniphila
14. line 219, 278: Junhong Su ---- Su
15. line 222, 232: Ikram Ali ---- Ali
16. line 223: people ---- people (36)
17. line 238, probiotic treatment: Microbial genus/species of probiotics need to be described.
18. line 238: Bifidobacteria (italic type) --- Bifidobacterium (italic type)
19. line 239: Cluster IV (italic type) ---- cluster IV (roman type)
20. line 240: Cluster XIVa (italic type) ---- cluster XIVa (roman type)
21. line 250: and (italic type) ---- and (roman type)
22. line 257: 25 days). ---- 25 days) (30).
23. line 257: prevotella_9 and prevotella_2 ---- Prevotella_9 and Prevotella_2
24. line 255: What is the meaning of Ellin516?
25. line 273: Proteobacterium ---- Proteobacteria
26. line 281: fasting ---- fasting (34)
27. line 287: producers ---- producers (35)
28. line 290: IFNg+ ---- IFNgamma+
29. line 290: TNFa- ---- TNFalpha –
30. line 290: Full spelling of MAITs needs to be written.
31. line 292: IF ---- IF (39)
32. line 298: Full spelling of HOMA-IR needs to be written.
33. line 299: Neisseria dentiae ---- N. dentiae
34. line 323: spp (italic type), phylum (italic type) ---- spp (roman type), phylum (roman type)
35. line 360: Ruminococcus gnavus ---- R. gnavus
36. line 393: phylum (italic type) ----- phylum (roman type)
37. line 416: Clostridium (roman type) ---- Clostridium (italic type)
38: Titles of References 1, 2, 8, 17, 18, 20, 21, 22, 28, 32, 36, 38, 39, 40, 48, 51, 52, 55, 56, 57, 61: The use of capital letters is not correct. Please refer to reference 3.
39. References 8, 28, 32, 56, 57: The names of bacteria should be written in italic type.
40. Table 1: Yan He ---- He, Zeb F ---- Zeb, Junhong Su ----- Su, Iklam Ali ---- Ali, Stanislawski Ma ---- Stanislawski, Guo Y ---- Guo
41. Table 1, Measurement of the gut microbiome: Description should be shortened. Additional explanation needs to be added in the footnote.
42. Table 2: Yan He ---- He, Zeb F ---- Zeb, Junhong Su ----- Su, Iklam Ali ---- Ali, Stanislawski Ma ---- Stanislawski, Guo Y ---- Guo
43. Table 3: Yan He ---- He, Zeb F ---- Zeb, Junhong Su ----- Su,
44. Supplement Table S2: Yan He ---- He, Iklam Ali ---- Ali, Guo Y ---- Guo

Mail FK UNDIP

Adriyan Pramono <adriyanpramono@fk.undip.ac.id>

Bioscience of Microbiota, Food and Health - Manuscript ID BMFH-2023-111.R1

1 pesan

Bioscience of Microbiota, Food and Health <onbehalfof@manuscriptcentral.com> 11 Maret 2024 pukul 10.49

Balas Ke: bmfh@ipec-pub.co.jp
Kepada: adriyanpramono@fk.undip.ac.id

11-Mar-2024

Dear Dr. Pramono:

Your manuscript entitled "Intermittent Fasting Modulates the Human Gut Microbiota Diversity in Phenotype Dependent Manner: A Systematic Review" has been successfully submitted online and is presently being given full consideration for publication in the Bioscience of Microbiota, Food and Health.

Your manuscript ID is BMFH-2023-111.R1.

Please mention the above manuscript ID in all future correspondence or when calling the office for questions. If there are any changes in your street address or e-mail address, please log in to Manuscript Central at https://mc.manuscriptcentral.com/bmfh and edit your user information as appropriate.

You can also view the status of your manuscript at any time by checking your Author Center after logging in to https://mc.manuscriptcentral.com/bmfh.

Due to the continued spread of SARS-CoV-2, many of our Editors and Reviewers are facing increased pressures and disruption from the closure of universities and movement to online-teaching. As such, the peer review process may take slightly longer than usual. We appreciate your patience and understanding during this time.

Thank you for submitting your manuscript to the Bioscience of Microbiota, Food and Health.

Sincerely,
Bioscience of Microbiota, Food and Health Editorial Office

Reviewer #1
We would like to thank the editor and reviewers for their critical evaluation of our manuscript and the constructive comments that helped us improve it. We have addressed all points raised by the referees, as explained below in our point-by-point response to the reviewers' comments.

Response to comments Reviewer #1
We would like to thank this reviewer for his/her remark that this is a very interesting paper in a hot area of gut microbiota research, with particular interest in the effect of intermittent fasting on the gut microbiota using a systematic review approach.
.
We are pleased that this reviewer appreciates that our findings are relevants to determine how intermittent fasting may affect the gut microbiota in distinc phenotypes in human.

1. **About graphical abstract - We do not accept "Graphic Abstract". Therefore, if the figure is necessary, the authors need to add it as Figure 2 in the text.**
   We agree the suggestion of the reviewer. Therefore, we have removed the graphical abstract into the figure 2 of the manuscript.

2. **line 76: spp (italic type) ---- spp (roman type)**
   We agree the suggestion of the reviewer. Therefore, we have edited based on reviewer's suggestion the manuscript (we highlight with yellow mark).

Mail FK UNDIP

Adriyan Pramono <adriyanpramono@fk.undip.ac.id>

Bioscience of Microbiota, Food and Health - Decision on Manuscript ID BMFH-2023-111.R1

2 pesan

Bioscience of Microbiota, Food and Health <onbehalfof@manuscriptcentral.com> 23 Maret 2024 pukul 14.33

Balas Ke: skamiya@ks.kyorin-u.ac.jp
Kepada: adriyanpramono@fk.undip.ac.id

23-Mar-2024

Dear Dr. Pramono:Manuscript ID BMFH-2023-111.R1 entitled "Intermittent Fasting Modulates the Human Gut Microbiota Diversity in Phenotype Dependent Manner: A Systematic Review" which you submitted to the Bioscience of Microbiota, Food and Health, has been reviewed. The comments of the reviewer(s) are included at the bottom of this letter.

The manuscript has been revised according to the comments from the referee. Further comments were pointed out by the referee. The authors are requested to revise it again according to the comments from the referee.

The reviewer(s) have recommended publication, but also suggest some minor revisions to your manuscript. Therefore, I invite you to respond to the reviewer(s)' comments and revise your manuscript.

To revise your manuscript, log into https://mc.manuscriptcentral.com/bmfh and enter your Author Dashboard, where you will find your manuscript title listed in "Manuscripts with Decisions." Click on "Create a Revision." Your manuscript number has been appended to denote a revision.

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Please also highlight the changes to your manuscript within the document by using the track changes mode in MS Word or by using bold or colored text.

Once the revised manuscript is prepared, you can upload it and submit it through your Author Center.

When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) in the space provided. You can use this space to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Because we are trying to facilitate timely publication of manuscripts submitted to the Bioscience of Microbiota, Food and Health, your revised manuscript should be uploaded as soon as possible. If it is not possible for you to submit your revision in a reasonable amount of time, we may have to consider your paper as a new submission.

Once again, thank you for submitting your manuscript to the Bioscience of Microbiota, Food and Health and I look forward to receiving your revision.

Sincerely,
Dr. Shigeru Kamiya
Editor in Chief, Bioscience of Microbiota, Food and Health
skamiya@ks.kyorin-u.ac.jp

[Editor's Comments]
Editor
Comments to the Author:
The authors need to revise the manuscript again according to the comments from the reviewer.

[Reviewer(s)' Comments]
Reviewer: 1

Comments to the Author
The manuscript has been revised according to my comments, but the following minor points need to be corrected.

1)line 238: Lactobacillus plantarum ---- Lactiplantibacillus plantarum
2)line 239: Lactobacillus rhamnosus ----- Lacticaseibacillus rhamnosus
3)line 258: bacterium Ellin 516 (italic type) ------ bacterium Ellin 516 (roman type)
4)line 327: phylum (italic type) ---- phylum (roman type)
5)line 503: akkermansia (italic type) ------ Akkermansia (italic type)
6)line 555: akkermansia (italic type) ------ Akkermansia (italic type), bacteroides (italic type) ----- Bacteroides (italic type)
7)line 567: faecalibacterium (italic type) ---- Faecalibacterium (italic type)
8)line 590: firmicutes/bacteroidetes (roman type) ----- Firmicutes/Bacteroidetes (roman type)

Adriyan Pramono <adriyanpramono@fk.undip.ac.id> 24 Maret 2024 pukul 11.46
Kepada: Ferbian Milas Siswanto <ferbian.siswanto@atmajaya.ac.id>
Bcc: Adriyan Pramono <adriyanpramono@fk.undip.ac.id>

Dear Dr. Ferbian

Melalui email ini saya teruskan komentar revisi minor dari BMFH.

Sekaligus, saya lampirkan hasil revisi saya dalam .zip. Untuk revisi dalam manuskrip saya highlight kuning. Kemudian minor rebuttal letter nya saya sertakan juga.
Semua file revisi ada dalam folder terkompres.

Demikian saya mengucapkan terima kasih atas kerjasamanya.

Salam,
Adriyan

Adriyan Pramono, PhD.

Assistant Professor
Department of Nutrition Science,
Faculty of Medicine,
Diponegoro University, Indonesia.
Center of Nutrition Research/CENURE (Chair).
ORCID: https://orcid.org/0000-0003-2159-4576
[Kutipan teks disembunyikan]

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minor rev24March2024 (2).zip
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Adriyan Pramono <adriyanpramono@fk.undip.ac.id>

Bioscience of Microbiota, Food and Health - Manuscript ID BMFH-2023-111.R2

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Bioscience of Microbiota, Food and Health <onbehalfof@manuscriptcentral.com> 24 Maret 2024 pukul 12.16

Balas Ke: bmfh@ipec-pub.co.jp
Kepada: adriyanpramono@fk.undip.ac.id

24-Mar-2024

Dear Dr. Pramono:

Your manuscript entitled "Intermittent Fasting Modulates the Human Gut Microbiota Diversity in Phenotype Dependent Manner: A Systematic Review" has been successfully submitted online and is presently being given full consideration for publication in the Bioscience of Microbiota, Food and Health.

Your manuscript ID is BMFH-2023-111.R2.

Please mention the above manuscript ID in all future correspondence or when calling the office for questions. If there are any changes in your street address or e-mail address, please log in to Manuscript Central at https://mc.manuscriptcentral.com/bmfh and edit your user information as appropriate.

You can also view the status of your manuscript at any time by checking your Author Center after logging in to https://mc.manuscriptcentral.com/bmfh.

Due to the continued spread of SARS-CoV-2, many of our Editors and Reviewers are facing increased pressures and disruption from the closure of universities and movement to online-teaching. As such, the peer review process may take slightly longer than usual. We appreciate your patience and understanding during this time.

Thank you for submitting your manuscript to the Bioscience of Microbiota, Food and Health.

Sincerely,
Bioscience of Microbiota, Food and Health Editorial Office

Response to comments Reviewer #1

The manuscript has been revised according to my comments, but the following minor points need to be corrected.

We would like to thank the reviewer for positive evaluations of our manuscript.
According to the reviewer's suggestions, we have revised point-by-point as described below:

1)line 238: Lactobacillus plantarum ---- Lactiplantibacillus plantarum
We have revised according to reviewer's suggestion as written *Lactiplantibacillus* plantarum in the yellow highlight

2)line 239: Lactobacillus rhamnosus ----- Lacticaseibacillus rhamnosus
We have revised according to reviewer's suggestion as written *Lacticaseibacillus* rhamnosus in the yellow highlight

3)line 258: bacterium Ellin 516 (italic type) ------ bacterium Ellin 516 (roman type)
We have revised according to the reviewer's suggestion as written … bacterium Ellin 516 in the yellow highlight

4)line 327: phylum (italic type) ---- phylum (roman type)
We have revised it according to the reviewer's suggestion as written … phylum in the yellow highlight

5)line 503: akkermansia (italic type) ------ Akkermansia (italic type)
We have revised according to the reviewer's suggestion as written …*Akkermansia* in the yellow highlight

6)line 555: akkermansia (italic type) ------ Akkermansia (italic type), bacteroides (italic type) ----- Bacteroides (italic type)
We have revised according to the reviewer's suggestion as written …*Akkermansia* and *Bacteroides* in the yellow highlight

7)line 567: faecalibacterium (italic type) ---- Faecalibacterium (italic type)
We have revised it according to the reviewer's suggestion as written … *Faecalibacterium* in the yellow highlight

8)line 590: firmicutes/bacteroidetes (roman type) ----- Firmicutes/Bacteroidetes (roman type)
We have revised according to the reviewer's suggestion as written … Firmicutes/Bacteroidetes in the yellow highlight

Mail FK UNDIP

Adriyan Pramono <adriyanpramono@fk.undip.ac.id>

Bioscience of Microbiota, Food and Health - Decision on Manuscript ID BMFH-2023-111.R2

1 pesan

Bioscience of Microbiota, Food and Health <onbehalfof@manuscriptcentral.com> 11 April 2024 pukul 07.56

Balas Ke: skamiya@ks.kyorin-u.ac.jp
Kepada: adriyanpramono@fk.undip.ac.id

11-Apr-2024

Dear Dr. Pramono:

It is a pleasure to accept your manuscript entitled "Intermittent Fasting Modulates the Human Gut Microbiota Diversity in Phenotype Dependent Manner: A Systematic Review" in its current form for publication in the Bioscience of Microbiota, Food and Health. The comments of the reviewer(s) who reviewed your manuscript are included at the foot of this letter.

Thank you for your fine contribution. On behalf of the Editors of the Bioscience of Microbiota, Food and Health, we look forward to your continued contributions to the Journal.

Sincerely,
Dr. Shigeru Kamiya
Editor in Chief, Bioscience of Microbiota, Food and Health
skamiya@ks.kyorin-u.ac.jp

[Editor's Comments]
Editor
Comments to the Author:
After minor revision, the revised manuscript is now worth reporting in the journal.

[Reviewer(s)' Comments]
Reviewer: 1

Comments to the Author
The manuscript has been revised according to the comments from the referee. It is now acceptable for publication in the journal.

Mail FK UNDIP

Adriyan Pramono <adriyanpramono@fk.undip.ac.id>

Bioscience of Microbiota, Food and Health - Please prepare and submit your final data for BMFH-2023-111.R2

2 pesan

Bioscience of Microbiota, Food and Health <onbehalfof@manuscriptcentral.com> 18 April 2024 pukul 12.01
Balas Ke: bmfh@ipec-pub.co.jp
Kepada: adriyanpramono@fk.undip.ac.id

18-Apr-2024

BMFH-2023-111.R2 - Intermittent Fasting Modulates the Human Gut Microbiota Diversity in Phenotype Dependent Manner: A Systematic Review

Dear Dr. Pramono:

Our native English proofreader has proofread your manuscript and the corrections and comments are as per attached.
Please check and correct where necessary and upload your corrected final version of your manuscript files.
We will proceed to advance publication online on J-STAGE once we receive your final manuscript files.

You will find your manuscript in your author center under the list "Manuscripts Accepted for First Look".

Sincerely,
bmfh@ipec-pub.co.jp
Bioscience of Microbiota, Food and Health

BMFH-2023-111.docx
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Adriyan Pramono <adriyanpramono@fk.undip.ac.id> 21 April 2024 pukul 12.35
Kepada: Ferbian Milas Siswanto <ferbian.siswanto@atmajaya.ac.id>
Bcc: Adriyan Pramono <adriyanpramono@fk.undip.ac.id>

Dear Dr. Ferbian

Bersama ini saya lampirkan final proof dari jurnal BMFH.
Saya sudah editing sesuai input mereka.

Saya minta tolong dibantu final check oleh mas Ferbian.
Terima kasih

Atas perhatian dan kerjasamanya saya mengucapkan terima kasih.

Salam,
Adriyan

Adriyan Pramono, PhD.

Assistant Professor
Department of Nutrition Science,
Faculty of Medicine,
Diponegoro University, Indonesia.
Center of Nutrition Research/CENURE (Chair).
ORCID: https://orcid.org/0000-0003-2159-4576
[Kutipan teks disembunyikan]

2 lampiran

BMFH-2023-111.docx
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Intermittent Fasting Modulates ~~the~~ Human Gut Microbiota Diversity in a ~~Phenotype~~ Phenotype-~~Dependent~~ dependent Manner: A Systematic Review

Adriyan Pramono[1,2*], Martha Ardiaria[1,2], Edward Kurnia Setiawan Limijadi[3], Etika Ratna Noer[1,2], Endang Sri Lestari[4], ~~,~~ and Ferbian Milas Siswanto[5]

Affiliations:

[1]Department of Nutrition Science, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia

[2]Center of Nutrition Research (CENURE), Nutrition and Metabolism Research Group

[3]Department of Clinical Pathology, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia

[4]Department of Medical Microbiology, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia

[5]Department of Chemistry and Biochemistry, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Jakarta, Indonesia.

*Address to correspondence: Dr. Adriyan Pramono

Email: adriyanpramono@fk.undip.ac.id

Word count: 4739 (without abstract, tables, figures, and references)

ABSTRACT

Cumulative evidence suggests that intermittent fasting (IF) has beneficial effects on human metabolic health. It has been indicated that its impact on the gut microbiota may mediate these beneficial effects. As a result, we hypothesized that IF may impact the human gut microbiota. A systematic review was carried out ~~following~~ according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) protocol using ~~databases:~~ the PubMed, Scopus, and CINAHL databases. We registered our systematic review protocol ~~on~~ in PROSPERO ~~with~~ under registration number CRD42021270050. Human intervention studies published until April 30~~th~~, 2023, were included. The quality of the included studies was assessed using National Institutes of Health (NIH) quality assessment study tools for intervention studies. The search in the database returned 166 studies, of which 13 matched all criteria for the final qualitative analysis. The body of evidence suggests that IF modulates human gut microbiota alpha and beta diversity in lean (relatively healthy) and relatively healthy overweight/obese individuals but not in individuals with metabolic syndrome. Furthermore, IF also alters human gut microbiota composition in all phenotypes. Of interest, the gut microbiota taxa or microbial metabolites after an IF intervention are associated with ~~the~~ metabolic markers. According to this review, IF influences the diversity and taxonomic levels of the human gut microbiota. Individual metabolic phenotypes may alter the effect of IF on the diversity and taxonomic levels of the gut microbiota.

Key words: intermittent fasting~~;~~ , gut microbiota~~;~~ , diversity~~;~~ , human~~;~~ , systematic review

List of Abbreviations

Abbreviation	Meaning
ATP	Adenosine ~~Triphosphate~~triphosphate
BMI	Body ~~Mass~~ mass ~~Index~~index
BCAA	Brain-chain amino acids
DASH ~~Diet~~diet	Dietary Approaches to Stop Hypertension ~~Diet~~diet
DNA	Deoxyribonucleic ~~Acid~~acid
HGC	High gene count
IF	Intermittent fasting
LGC	Low gene count

PICOS	Population, Intervention, Comparison/Control, Outcome, Study Design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
RCT	Randomized ~~Controlled~~ controlled ~~Trial~~trial
qPCR	Quantitative polymerase ~~Chain~~ chain ~~Reaction~~reaction
SCFAs	Short-chain fatty acids
T2D	Type 2 diabetes
TRF	Time-restricted feeding

Introduction

The human body ~~is~~ has a distinctive form made up of human cells and microorganisms [1]. It has been shown that a complex ecological community of microbiomes co~~-~~exists with the human ecosystem [2]. Cumulative evidence suggests that the gut microbiome affects host physiology and metabolism [3]. The gut microbiota is an ecosystem that includes all bacterial species that colonize the gastrointestinal tract permanently, as well as a huge number of additional microorganisms from the environment [4]. Firmicutes (which contains primarily the *Clostridium, Enterococcus, Lactobacillus*, and *Faecalibacterium* genera) and Bacteroidetes (which includes notably the *Bacteroides* and *Prevotella* genera) dominate the gut microbiota of a healthy human adult. Actinobacteria (primarily *Bifidobacterium*), Proteobacteria, Verrucomicrobia, and Euryarchaeota are represented in lower numbers [5].

A review by Lynch and Pederson described how gut microbiome diversity has been linked to the health and diseases of the host [2]. ~~The~~ An *in vivo* animal model ~~in vivo, as well as~~ and human studies~~,~~ support~~s~~ the link between the microbiome and metabolic diseases, such as obesity [6], type 2 diabetes (T2D) [7], insulin resistance [8], and hypertension [9]. The gut microbiota may influence host metabolism through a variety of mechanisms. ~~Among t~~These mechanisms include the synthesis of microbial metabolites of short-chain fatty acids (SCFAs) [10] and the balance between the gut microbiota and immune system [11]. ~~Another~~ Other example~~s~~ ~~is~~ include the role of the gut microbiota in the synthesis of micronutrient~~s synthesis~~ such as vitamins, which are of great value for both microbial and host metabolisms, and its essential role in the co-metabolism of bile acids with the host [12].

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The normal gut microbiota performs particular functions in host nutrition metabolism, xenobiotic and drug metabolism, gut mucosal barrier structural integrity, immunomodulation, and pathogen defense. A number of factors influence the normal gut microbiome. These include (1) mode of delivery (vaginal or caesarean~~);~~), (2) food throughout infancy (breast milk or formula feeds~~);~~), and (3) use of antibiotics or antibiotic-like compounds originating from the environment or the gut commensal community [13]. It has been proposed that a greater composition, diversity, and functionality [14] of species associated with the production of SCFAs [10] (e.g., *Faecalibacterium prausnitzii*, *Bacteroides* spp., *Bifidobacterium* spp.) are perhaps the hallmarks of a microbial community associated with better health outcomes. However, peptide and protein fermentation in the gut (proteolytic fermentation) may produce primarily toxic chemicals, such as ammonia, phenols, and branched-chain fatty acids. These may be harmful to the host's digestive and metabolic health~~.~~ [10].

A comprehensive review by Singh et al. ~~has~~ indicated the effects of dietary intake/components on the gut microbiome [15]. In addition, there has been ~~a~~ growing interest in identifying alternative dietary modifications that involve restricting energy intake to specific periods of the day or prolonging the fasting interval between meals, called intermittent fasting (IF) [16, 17]. Time-restricted feeding (TRF), a type of IF, is the only eating pattern that does not necessitate calorie restriction [17]. Regarding TRF, religious fasting, which can be found in several religions ~~[~~(e.g., Ramadan fasting ~~with~~in Islam, which has been recognized for its similarities to ~~the~~ TRF~~]~~), could also be considered a form of TRF [18].

IF is one of the diet regimens that may also promote fat mass loss, reduce body weight, and improve metabolic health [19]. ~~The m~~Modulation of the gut microbiota may mediate these beneficial effects. ~~Fasting~~ There is evidence (primarily from rat models) suggesting that fasting ~~appears to~~ affects the gut microbiome~~, according to evidence (primarily from rat models)~~ [20-23]. Given the apparent role of IF and the microbiome in human metabolic health, we assumed that IF influences the diversity and (relative) abundance of distinct bacterial taxa in the human gut microbiota, as well as their functionality, in humans.

Material and Methods

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [24] and is registered in the PROSPERO database under registration number **CRD42021270050**.

Search strategy

Three electronic databases (PubMed, Scopus, and CINAHL) were screened for original articles published up to December 31st, 2021 (updated on April 30th, 2023), using the following main keywords: “intermittent fasting,” “Ramadan fasting,” “time-restricted feeding,” “time-restricted eating,” “time-restricted fasting,” “gut microbiome,” “gut microbiota,” “gut microflora,”

Commented [SB1]: Here is an alternative phrasing that avoids the use of the abbreviation e.g.:

such as *Faecalibacterium*

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such as Ramadan

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theorized
OR
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and "gut bacteria." These keywords were combined using the Boolean operators AND~~,~~ and OR~~,~~ and constructed for each database. The specific combinations of keywords used for the searches in each database ~~is~~ are listed in **Supplemental Table S1**. In addition, relevant ~~titles~~ articles from previously published reviews ~~will be~~are reviewed under ~~each~~ the subject ~~category~~categories below. Only articles published in English were eligible. The reference lists of ~~the established~~previous reviews and articles were further checked for additional articles.

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Study selection, inclusion, and exclusion

The PICOS (Population, Intervention, Comparison/Control, Outcome, Study Design) framework was used to develop inclusion criteria. ~~Population~~ The population (P) included in this study ~~were~~ comprised adults (≥ 18 years) with no specific criteria for body mass index (BMI~~) (~~; in kg/m^2). The intervention (I) ~~consists of~~was any type~~s~~ of IF as described by Petterson and Sears [25] (including complete alternate-day fasting, modified fasting regimens, time-restricted feeding, religious fasting, Ramadan fasting, and other religious fasting). No minimum intervention duration criterion was applied. The primary outcome (O) was a measure of the gut microbiome, including (but not limited to)~~:~~ alpha diversity (a measure of variability within a sample~~);~~), beta diversity (a measure of between-sample variability in microbial composition~~);~~), species richness~~;~~ , any prevalence or (relative) abundance of bacterial taxa,~~;~~ Firmicutes/Bacteroidetes ratio~~;~~ , and functions of the gut microbiome. The secondary outcome was gut microbiota metabolites.

We only included human studies that were published in an English-language, peer-reviewed journal. Electronic items were permitted ahead of print. Reviews, editorials, letters, and comments were not considered due to the fact that they lacked original data. Conference abstracts and protocols were also omitted, as they had not undergone the same level of peer review as full-text articles. Two authors (AP and MA) separately assessed abstracts and complete texts for eligibility, with any doubts about eligibility discussed among the authors.

Data extraction and synthesis

Two authors (AP and MA) extracted data using standardized forms, including study characteristics, PICOS details, biological specimen~~(s)~~ and techniques used to assess the microbiome, and all intervention-outcome effect~~s~~ measures. The characteristics of each included article~~s~~, such as references, study design, ethnicity, and ~~the~~ number of participants, were included in the intervention and control groups. Furthermore, the details included patient characteristics (age, BMI, % female, comorbidities), descriptions of ~~the~~ interventions (type of IF and duration), comparisons, and settings (laboratory or free~~-~~ living). Other details included outcomes (the primary outcome was gut microbiome diversity and composition; the secondary outcome was gut microbiota-derived metabolites) and durations of follow-up.

Quality assessment

The authors applied a previously reported tool created by the National Heart, Lung, and Blood Institute in the United States ~~(US)~~ to assess ~~the~~ a study's quality. This original assessment form was adopted ~~since~~ because it has previously been utilized in controlled trials and single-group intervention studies [26]. Four assessment items represented fatal flaws if the answers for the following criteria were~~ed~~ "~~No~~no/~~N~~not reported/~~Can't~~ can't determine" ~~for these following criteria~~: 1~~.~~) ~~R~~randomization~~;~~ , 2~~.~~) ~~Dropout~~ dropout rate of less than 20~~%;~~ %, 3~~.~~) ~~Valid~~valid/reliable outcome measures, and 4) intent-to-treat analysis in random/cross-over trials. For single-group interventions, the criteria were 1~~.~~) ~~Eligibility~~ eligibility criteria pre-specified~~;~~, 2~~.~~) ~~A~~adequate sample size~~;~~, 3~~.~~) ~~V~~valid/reliable outcome measures~~;~~, and 4~~.~~) ~~D~~dropout rate of less than 20% or intent-to-treat analysis. ~~Global~~ A global rating was determined based on the number of fatal flaws: good quality (0 fatal flaws), acceptable quality (1 fatal flaw), or poor quality (≥2 fatal flaws). Quality assessment was conducted independently by two reviewers (AP and MA). Any disagreement between the reviewers was resolved through discussion (with the third author, EKSL).

Results

Characteristics of the included studies

Figure 1 shows an article identification, screening, and final selection flow chart. The search identified 166 unique publications. Following the removal of articles with duplicate titles and full-text screening, the authors included 13 studies [27-39] in this systematic review.~~–~~ The characteristics of the included studies are summarized in **Table 1.**

Table 1 shows the characteristics of the included studies concerning the populations/participants, age, nutritional status (e.g., ~~body mass index/~~BMI), sex, sample size, type of fasting interventions, duration, and ~~the~~ methodology used to ~~determine~~ perform the gut microbiome analysis. Eight studies enrolled healthy participants [27-30, 33, 34, 36, 37], three studies were performed on overweight or obese people [31, 32, 38], and two studies enrolled individuals with metabolic syndrome [35, 39]. Several types of IF were used in the included studies. Four studies [32, 35, 38, 39] used an IF with or without modification, such as ~~(for example, when~~ pair~~ed~~ing it with ~~the~~ a Dietary Approaches to Stop Hypertension (DASH) ~~D~~diet. Furthermore, five ~~research~~ studies [28, 33, 34, 36, 37]~~,~~ evaluated the effects of Ramadan fasting on the gut microbiota, while one study [25] investigated the effect of Buchinger fasting on the gut microbiota [27]. Other studies ~~have~~ reported the effect of TRF only (2 studies~~,~~) [30, 31]~~)~~. The durations of the interventions in the included trials ranged from 7 days to one and a half years [27-39]. ~~The m~~Microbiome characteristics were reported in all of these studies, including ~~the~~ diversity, changes, or both ~~in~~ at the gen~~era~~us, phylum, and species levels. A few studies also reported on the impact of fasting on the levels of gut microbiota metabolites such as ~~short-chain fatty acid (~~SCFAs~~) levels~~.

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such as BMI

Qualitative analysis of the effects of fasting on the gut microbiota

~~The e~~Effect of IF on the gut microbiota's alpha-beta diversity

In general, the majority of the included studies (8 out of 13) found significant differences in microbial diversity between baseline and after their interventions (key findings are shown in **Table 2**). Two studies did not analyze gut microbiota diversity in their research. Meanwhile, three other studies found no changes in microbial diversity following IF regimens. Changes in microbial diversity (alpha and beta diversity) were detected after Ramadan fasting [33, 34, 36] and IF/TRF [27, 29, 30, 32, 38].

~~The~~ Comparison of the effect of IF on ~~the~~ gut microbiota diversity between metabolic phenotypes

The investigations with lean (relatively healthy) and overweight or obese participants demonstrated consistent changes in beta diversity, as described in **Table 3**. In terms of alpha diversity change, inconsistent results were obtained for both lean (relatively healthy) and overweight or obese people ~~revealed inconsistent results~~. Two fasting studies (Mesnage et al. [27] and Ozkull et al. [33]), reported no change in alpha diversity. It could be that these two studies performed their fasting interventions in individuals with similar characteristics to the population with regard~~s~~ to dietary patterns and that they ~~have~~ had already gotten used to ~~these~~ the types of IF that were used.~~–~~

Surprisingly, we did not see any alpha or beta diversity changes after IF interventions in adult individuals with metabolic syndrome. These findings may imply that the metabolic phenotype of the individual~~s~~ influences the outcome ~~of the~~for gut microbiota diversity ~~due to~~after IF.

~~The e~~Effect of IF on ~~the~~ gut microbiota composition

~~Thirteen~~ The 13 included human intervention studies ~~have~~ show~~n~~ed that fasting altered the gut microbiota at the phylum, genus, or species level~~s~~. Details of the outcomes of interest are reported in **Table 3**. There is clear evidence showing that any fasting intervention can modulate~~d~~ the bacterial community composition. The majority of the studies reported that Firmicutes is upregulated following a fasting intervention. Mesnage et al. showed that ten days of Buchinger fasting resulted in a decreased abundance of *Lachnospiraceae* and *Ruminococcaceae* [27]. However, an increase in Bacteroidetes and Proteobacteria was observed in that study [27]. Ozkul et al. reported that Firmicutes, *Akkermansia muciniphila*, and *Bacteroides fragilis* were significantly increased after Ramadan fasting [28] in Caucasians. In another study, Ozkul et al. reported similar findings compared ~~to~~ with their previous findings [33]. Furthermore, they showed that Firmicutes had a relatively higher abundance than Bacteroidetes after Ramadan fasting. In addition, they found that *Butyricicoccus pullicaecorum, F. prausnitzii,* and *Roseburia* were the primary species that were significantly increased within the Firmicutes phylum after Ramadan fasting in Caucasian volunteers [33].

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Effect of IF on the gut microbiota diversity according to metabolic phenotype

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characteristics similar to those of the general population with regard to dietary patterns

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Butyricicoccus pullicaecorum, F. prausnitzii, and *Roseburia* species were the primary species that were significantly increased within the Firmicutes phylum OR
the primary species and genus that were significantly increased within the Firmicutes phylum were *Butyricicoccus pullicaecorum, F. prausnitzii*, and *Roseburia*

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Changes in ~~the~~ dietary patterns during fasting have been suggested to shape the gut microbiota diversity and abundance. However, some, but not all, types of fasting~~,~~ do not rule out the possibility that ~~the~~ dietary patterns may not be changed. For example, Ramadan fasting is a type of IF that requires refraining from food and drink from dawn to sunset. Another method of IF is to limit mealtimes to 8 hours followed by 16 hours of fasting ~~time~~ [30]. The beta-diversity of the gut microbiota in the present review study showed consistent changes between these two types of IF; primarily, the Firmicutes phylum, which were increased significantly in Ramadan fasting interventions [28, 33, 34, 36, 37] followed by an increase in *Lachnospiraceae*, *Ruminococcaceae*, *B. pullicaecorum*, *F. prausnitzii*, *Roseburia* (5), and an increase in *A. mu~~n~~ci~~e~~niphila* [28, 33].

Su et al. reported similar findings, ~~where~~ with the phylum Firmicutes ~~was~~ upregulated and the phylum Bacteroides, especially the family *Prevotellaceae*, ~~were~~ reduced following Ramadan fasting to a similar extent between young and middle-aged volunteers [34]. According to Ali et al., the abundance of Bacter~~i~~oidetes decreased after fasting during Ramadan in Chinese people, while the abundance of Proteobacteria increased ~~after fasting during Ramadan in Chinese people~~ [36]. In contrast, in Pakistani individuals, the abundance of Bacteroidetes increased after Ramadan fasting, whereas that of Firmicutes decreased ~~after Ramadan fasting~~ [36]. Similar results have been shown for a Buchinger's fasting intervention [27]. ~~Another~~ In another Ramadhan fasting study, ~~by~~ Mohammadzadeh et al. showed that *Bacteroides* and Firmicutes were significantly increased during Ramadan fasting [37]. Overall, in this systematic review, we found consistent results about the effects of Ramadan fasting on gut microbiota composition. Ramadan fasting influences the gut microbiota composition in lean (relatively healthy) or overweight/obese individuals. However, the change in gut microbiota composition after Ramadan may also be influenced by the distinct dietary patterns of each ethnicity, at least as indicated by Ali et al. [36].

A modified IF (water-only fasting vs. juice-only fasting) ~~indicated~~ suggested that water-only fasting dramatically changed the bacterial community. Individually, the relative abundance of *Fusobacterium* was reduced in four participants who harbored higher *Fusobacterium* prior to fasting compared ~~to~~ with the other two participants. Post-IF, *Fusobacterium* ~~remains~~ remained consistently low across all six individuals [29]. A pilot study of IF combined with laxative treatment for four weeks and probiotic treatment using capsules containing *Lactiplantibacillus plantarum*, *Streptococcus thermophiles*, *Lactobacillus acidophilus*, *Lacticaseibacillus rhamnosus*, *Bifidobacterium lactis*, *Bifidobacterium longum*, and *Bifidobacterium breve* for six weeks found that the abundances of *Bifidobacterium* and *Akkermansia* ~~was~~ were significantly increased~~,~~ but that the abundances of *Clostridium* cluster IV, *Clostridium* cluster XIVa, Bacteroidetes, and *Prevotella* ~~was~~ were ~~not~~ unchanged [32]. These findings suggest that both

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Commented [SB9]: The intended meaning of this is unclear, and it is ungrammatical in its current form. Also, it is unclear what is meant to be conveyed by the 5 after *Roseburia*. Here is an alternative phrasing that I thought might make sense for this, assuming that the 5 represents a reference citation:

IF, primarily in the Firmicutes phylum, which showed significant increases in Ramadan fasting interventions [28, 33, 34, 36, 37], but also in *Lachnospiraceae*, *Ruminococcaceae*, *B. pullicaecorum*, *F. prausnitzii*, *Roseburia*, and *A. muciniphila*, all of which also showed increases [5, 28, 33]

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medications (~~i.e., a~~ laxative ~~treatment or~~and a specific food type, ~~(~~i.e., a probiotic~~)~~) may have distinct effects on the IF-related gut microbiota composition.

~~Furthermore, t~~There were also substantial differences in the microbial composition within individuals during IF combined with a type of diet (~~i.e., the~~ DASH diet), reflecting a characteristic of intervention-induced shift, ~~which later~~with partial~~ly~~ rever~~ted~~sion following a 3-month refeeding period on a DASH diet. There was a significant shift in Firmicutes ~~shifted significantly in~~ abundance, with an initial decrease in *F. prausnitzii*, *Eubacterium rectale,* and *Coprococcus*~~, which further~~ that subsequently reverted after three months [35]. In a~~A~~ study that combined IF and lifestyle changes for three months, there were ~~resulted in~~ fluctuations in five bacterial genera ~~fluctuations~~ (*Subdoligranulum, Collinsella, Parabacteroides, Alistipes,* and *Bacteroides*). *Subdoligranulum* and *Collinsella* decreased in relative abundance, while the other three taxa increased. In that study, the baseline and three-month abundances were dominated by the phyla Firmicutes and Bacteroidetes [38]. Another IF intervention [39] in different ethnic groups was shown to increase the relative abundances of *Ruminococcus gnavus*, *Chitinophagaceae bacterium*, *Roseburia faecis*, *Paraburkholderia caribensis*, *Verrucomicrobiae* bacterium Ellin516, *Neisseria dentiae*, and *Streptococcus ferus* [39].

Zeb et al. found that 34 bacteria were enriched at the genus level following a TRF intervention (8 hours per day for 25 days) [30]. *Prevotellaceae* (*Prevotella_9* and *Prevotella_2*) and Bacteroidetes dominated the TRF group, while *Escherichia, Shigella,* and *Peptostreptococcus* were abundant ~~in~~ at the genus level in the non-TRF group [30]. In contrast, there was no significant alteration in the abundances of Firmicutes and Bacteroidetes after 12 weeks of TRF, despite Firmicutes and Bacteroidetes being the two most common phyla ~~of the~~based on total abundance at baseline, ~~which were~~with abundance ratios of 61.2% and 26.9%, respectively [31].

Qualitative analysis of the relationship between the gut microbiota or its metabolites and metabolic health in humans

This review also identified how the gut microbiota and its metabolites may be associated with metabolic health ~~from~~ based on the included studies. A Buchinger fasting study [27] showed that SCFA levels were ~~not~~ unchanged during fasting. However, the levels of serum brain-chain amino acids (BCAAs) were significantly increased during fasting and ~~were~~ significantly ~~declined~~ decreased after fasting. Interestingly, the abundance of *Lachnospiraceae (Coprococcus_2 eutactus, Fusicatenibacter saccharivorans,* and *Lachnospira pectinoschiza)* was positively associated with plasma glucose levels and ~~was~~ negatively associated with BCAA levels. In contrast, Bacteroidetes *(Bacteroides dorei/fragilis* and *Bacteroides thetaiotaomicron)*~~, as well as~~ and a Proteobacteria *(Bilophila wadsworthia)*~~,~~ presented the opposite trend and were negatively and positively associated with plasma glucose levels and BCAA levels, respectively [27]. Ozkul et al. reported that they did not find any association

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between bacterial composition and fasting glucose except for a negative correlation between *A. muciniphila* counts and fasting glucose ~~determined~~ after Ramadan fasting [28]. Ramadan fasting has been shown to upregulate bacterial butyrate producers [34, 36, 37]. More interestingly, at functional levels, Su et al. demonstrated that 29 pathways were present in ~~the~~ young individuals at the end of Ramadan fasting when contrasted with the pathways present at the start of fasting, whilst 14 pathways were present in their middle-aged cohort ~~at the end of Ramadan fasting when contrasted to pathways present at the start of fasting~~ [34]. The majority of the pathways presented were associated with host metabolism, genomics, and molecular signaling [34]. These findings indicate that any type of IF (i.e., Buchinger or Ramadan) ~~has~~ modulate~~d~~s ~~the~~ gut microbiota-derived metabolites, either SCFAs or BCAA. The duration of IF might differentially affect how ~~the~~ gut microbiota-derived metabolites are regulated, especially in those individuals who are overweight or obese.

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In addition, ~~the study by~~ Maifeld et al. showed that IF upregulates butyrate and propionate bacterial producers [35]. Moreover, they showed that in subjects with metabolic syndrome, ~~the~~ modulation of the gut microbiota composition, such as modulation of *E. rectale*, *Dorea longicatena,* and *Hungatella hathewayi* (acetate producers), was negatively correlated with IL-2-producing CD4+ T cells~~,~~ and the absolute number of IFNgamma+ and TNFalpha-producing mucosal-associated invariant T~~s~~ (MAIT~~s~~) cells, respectively [35]. Similarly, Guo et al. ~~have shown~~ showed that total plasma SCFAs in individuals with metabolic syndrome ~~was~~ are significantly increased after IF [39]. ~~The~~ This elevation remains significant after being adjusted for baseline SCFA levels [39]. More interestingly, based on the KEGG pathways, ~~after eight weeks of IF,~~ the altered gut microbiota was involved in "genetic information processing,"~~,~~ "environmental information processing,"~~,~~ and "metabolism" after eight weeks of IF ~~based on KEGG pathways~~. They also found a relationship between the abundances of twenty-three significantly altered gut microbial species and glucose metabolism, lipid profiles, and inflammatory cytokines, independent of weight loss. For instance, *Acidobacteria bacterium* and *Mitsuokella jalaludinii* showed the strongest positive association with ~~Homeostatic~~ homeostatic ~~Model~~ model ~~Assesment~~ assessment for ~~Insulin~~ insulin ~~Resistance~~ resistance (HOMA-IR), whereas *N. dentiae* was negatively related to serum glucose.

~~The q~~Quality of the included studies

Of the 13 included studies identified as relevant for this review, the methodological quality of one was rated as good; ten were classified as fair, and two were placed as poor. Regarding the prominent flaws, ten studies did not use randomized controlled designs~~;~~, two studies presented dropout rates above 20%, and ~~twelve~~ 12 studies did not perform an intent-to-treat analysis (**Supplemental Table S2**).

Discussion

Our systematic review found consistent effects of IF on the human gut microbiota, both on alpha and beta diversity. More interestingly, the alpha or beta diversity changes were different based on human metabolic phenotypes. There ~~is~~ was a constant shift in the alpha and beta diversity of the gut microbiome in lean participants (relatively healthy individuals)~~,~~ but not in adult overweight/obese participants with ~~overweight/obesity and~~ metabolic syndrome. Despite our findings ~~that~~ indicat~~e~~ing that IF influences gut microbiota diversity, we were unable to draw conclusions about the effect of IF on specific taxa (gut microbiota composition).

The variability in the studied populations (e.g., relatively healthy, overweight or obese, and metabolic syndrome populations), the duration**s** of the intervention**s**, the types of IF, the study design**s**, the methods used to assess the composition of the gut microbiome, and the data ~~analysis~~ analyses all play**ed** ~~a~~ role**s** in the synthesis of the results. Furthermore, hypervariable region analyses and sequencing platforms might have contributed to the ~~taxa's~~ variances in the abundance**s** of taxa. Two studies [29 and 38] did not provide alpha and beta diversity measurements as primary results; however, the~~re were~~ primary species that were significantly elevated (*B. pullicaecorum*, *F. prausnitzii*, *Roseburia species*) were ~~within~~ from the Firmicutes phylum following Ramadan fasting. According to both reports, *Bacteroides* spp. (Bacteroidetes phylum) were substantially more prevalent as compared ~~to~~ with the baseline levels.

Some of the included studies ~~have~~ also analyzed the association between changes in specific taxa after fasting and/or ~~its~~their metabolites with metabolic health parameters related to glucose metabolism, lipid metabolism, insulin sensitivity, and inflammation. Despite heterogeneity in the individual taxa studied, there is a link between the gut microbiota after fasting and metabolic health indices throughout Ramadan fasting. Adjustments for confounding, including ~~the~~ baseline values, were ~~conducted~~ made in all trials, with only a few studies adjusting for a limited number of confounders. Although the differences in taxonomic composition and functional potential varied across the studies, Firmicutes and ~~Bacteriodetes~~ Bacteroidetes were amongst the most consistently reported~~,~~ and were either upregulated or downregulated after fasting. In adults, it has been shown that Firmicute*s* largely dominate the gut microbiota, followed by Bacteroidetes [36]. Some studies in humans have shown that the gut microbiota of obese individuals exhibits a higher Firmicutes/Bacteroidetes ratio than that of normal-weight individuals~~,~~ and ~~proposing~~ proposed this ratio as an eventual biomarker. As a result, the Firmicutes/Bacteroidetes ratio is frequently cited in the scientific literature as a marker of obesity [40], although the underlying mechanisms remain unclear.

~~Changes~~ The changes in microbiota diversity in healthy subjects with lean (relatively healthy) bodies were consistently higher than those ~~of~~ in overweight or obese subjects with metabolic syndrome conditions. ~~Another~~ A previous systematic review showed that the baseline of the microbiota in obese individuals consists of a low abundance of *Lactobacillus, Bifidobacterium* [41], *F. prausnitzii, A. mu~~n~~c*i*e*n*iphila*, and increased *Prevotella* [42]. This may partly be

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such as relatively

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differences in the sequencing platforms and analyses of hypervariable regions

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It has previously been shown that the baseline microbiota in obese individuals has low abundances of *Lactobacillus*, *Bifidobacterium*, *F. prausnitzii*, and *A. muciniphila* and an increased abundance of *Prevotella* [41, 42].
OR
In their systematic review, Crovesy, Masterson, and Rosado found low abundances of *Lactobacillus* and *Bifidobacterium* in obese individuals at baseline [41]. Duan et al. further found low abundances of *F. prausnitzii* and *A. muciniphila* and an increased abundance of *Prevotella* in obese individuals at baseline [42].

explained by a high fat-carbohydrate diet and low fiber intake in individuals with obesity [43]. Lozupone et al. ~~A study~~ showed that consuming carbohydrate- or fat-restricted low-calorie diets for 1 year or high-fat/low-fiber or low-fat/high-fiber diets for 10 days induces statistically significant changes in the gut microbiota [44]. These baseline gut microbiota characteristics may explain the different responses in individuals with metabolic syndrome [35, 39] than in overweight or obese individuals [31, 32, 38] and healthy individuals after intermittent fasting [27-30, 33, 34, 36, 37].

~~A s~~Study of the gut microbiota and its function in obese and non-obese people has led to the idea of a high gene count (HGC) and low gene count (LGC), both of which have physiological and pathological implications. The defining characteristics of ~~the~~ an HGC microbiome in favor of digestive health include an increased number of butyrate-producing species, an increased proclivity for hydrogen production, the establishment of a methanogenic/acetogenic ecosystem, and a decrease in hydrogen sulfide production. Individuals with an HGC have a more functionally robust gut microbiome as well as a decreased prevalence of metabolic diseases and obesity. LGC individuals, on the other hand, have a larger number of pro-inflammatory bacteria, such as *Bacteroides* and *R. gnavus*. Furthermore, a few of the main bacterial metabolites in LGC individuals include modules for glucuronide degradation, aromatic amino acid degradation, and dissimilatory nitrite reduction, all of which are known to be hazardous [13, 45].

Several mechanisms may explain how IF influences the gut microbiota composition and metabolic health. During fasting, there is an increase in intestinal pH, there are changes in mucus production, and there is a decrease~~d~~ in intestinal capacity [46], which ~~that~~ could affect the microbial ecosystem. Furthermore, fasting also impacts changes in circadian rhythms via interactions between changes in the gut microbiota composition and gut-derived metabolites as signaling molecules to the peripheral and central clocks of the host [47]. Of interest is the interaction between circadian rhythms and gut microbes, which are intertwined via metabolic regulation, but the mechanisms that underlie their interactions are still not fully understood [48]. The dispositions and functions of microbes can fluctuate within a few hours depending on the timing of ~~the~~ a meal, which links the circadian rhythm of the host's behavior with diurnal fluctuations in the composition and function of the microbiota [49].

Furthermore, the beneficial effects of fasting may also be partly explained by an increase in fat oxidation during fasting. It is well established that the rate of carbohydrate utilization is decreased in the fasted state and that the increased rate of fat oxidation meets the energy demand ~~([~~[36]~~).~~]. On the other hand, it is also possible that the SCFAs produced by the gut microbiota ~~might be~~are used as a substrate (especially acetate in the overweight/obese phenotype) for host energy metabolism [50]. ~~Next to these~~In addition to this, intermittent fasting may ~~also~~ improve insulin regulation, resulting in ~~a~~ the ~~maintained~~ maintenance of glucose

Commented [SB15]: The meaning of this seems unclear. Here is an alternative phrasing that I thought possible for it:

gut-derived metabolites, which act as signaling molecules for the peripheral and central clocks

Commented [SB16]: Here is an alternative phrasing that I thought might make sense for this:

rate of fat oxidation increases to meet energy demands

metabolism, especially in overweight or obese individuals [51]. More interestingly, intermittent fasting may also activate the central metabolic regulation of ~~Sirtuins~~sirtuins, particularly SIRT1 and SIRT3. The activation of ~~Sirtuins~~ sirtuins by fasting can further exhibit their effects on insulin response, antioxidant defense, and glycolysis [52]. A recent review suggests that the effects of fasting on metabolism can be closely associated with alterations in the gut microbiota composition [53].

~~A~~ In their recent meta-analysis, ~~has~~Ejtahed et al. identified taxa associated with multiple diseases, including obesity [54]. In this review, the dominance of Firmicutes enrichment as an outcome after IF may be partly associated with an increase in endogenous substrates over a long fasting period [33]. In fact, fasting has been shown to increase endogenous SCFA production as an energy substrate for host metabolism [55], supported by an abundance of *B. pullicaecorum*-producing bacterial species of *F. prausnitzii* [32, 33]. Furthermore, the ~~quantity~~ abundances of the *Akkermansia* group and Verrucomicrobia phylum also consistently rise~~s~~ after fasting. The ability to dissolve mucin and the inherent features of the mucus layer might cause *A. muciniphila*~~it~~ to be resistant to environmental changes during fasting, therefore enriching the species group~~,~~ ~~which~~that includes *A. ~~municiphila~~muciniphila*. This species is essential for the proper functioning of intestinal barriers, and its presence defines a healthy gut profile [56, 57].~~—~~

~~During fasting,~~The metabolic changes during fasting include the dominant use of fatty acids as fuel for ~~the~~ synthesi~~s~~zing ~~of~~ adenosine triphosphate (ATP), reducing the fat mass, increasing functional capacity, and altering glucose homeostasis [58]. The negative correlation of *A. mu~~n~~ci~~en~~iphila* ~~to~~ with fasting glucose levels reinforces the positive effects on glucose regulation after Ramadan fasting [28]. Ramadan fasting also significantly increases butyrate, which can reduce the adverse effects of lipopolysaccharides and simultaneously increase the regulation of intestinal barrier function by stimulating mucin production [59]. In addition, butyrate also plays a role in the activation of G-protein receptors (GPR41 and GPR43) in the colon, stimulating the production of the hormone peptide YY (PYY) and glucagon-like peptide-1 (GLP-1), which further affects glucose homeostasis [60].

In several studies, Bacteroidetes were significantly increased after fasting. A possible mechanism ~~of~~ for Bacteroidetes elevation after fasting can be partly explained by the ~~consuming~~ consumption of vegetables and fruits in the diet [61], as shown in the Buchinger and Ramadan fasting studies [27, 28, 37]. Furthermore, the rapid tolerance/adaptation to the host environment during fasting ~~may~~ might also explain the higher ~~number~~ abundance of Bacteroidetes following fasting. Another ~~reason~~ possible explanation is its special ability to ~~replace~~ shift to a transcription profile with glycan derivatives when polysaccharide and glycoprotein supplies are depleted due to extended fasting [62]. Interestingly, both Buchinger and Ramadan fasting interventions gave consistent results in terms of the elevation of *F.*

Commented [SB17]: This is grammatical, but the phrasing seems odd. Specifically, this part: "The activation of sirtuins by fasting can further exhibit their effects…" Here are a couple of alternative phrasings that I thought might convey what was intended:

The activation of sirtuins by fasting can trigger further effects of them on the insulin response, antioxidant defense, and glycolysis [52].
OR
The activation of sirtuins by fasting allows them to exhibit effects on the insulin response, antioxidant defense, and glycolysis [52].

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Commented [SB18]: The intended meaning of this is unclear. Here is an alternative phrasing that I thought might make sense for this:

which is supported by the abundances of the butyrate-producing bacterial species *B. pullicaecorum* and *F. prausnitzii*

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prausnitzii (the dominant acetate producer of *Clostridium* cluster IV). Despite the fact that the composition of the gut microbiota varied across all investigations, the alterations in the microbiota composition ~~can~~ could reduce plasma lipopolysaccharide-binding protein and increase butyrate-producing bacteria.

~~In~~ For several types of fasting, including IF (Ramadan, time-restricted fasting), ~~the~~ a calorie-restriction fasting regimen ~~gives~~ provides an overview of the abundance and diversity shift of the gut microbiota taxonomy. However, there is a wide range of outcomes among them. ~~A~~In a TRF intervention, ~~is another~~a different type of IF regimen was used in which participants were provided food *ad libitum* ~~food~~ from 10:00 to 18:00 and fasted from 18:00 to 10:00 daily. There were no restrictions on the types or quantities of meals ingested throughout the eating window (8 hours), and participants were not required to track their calorie consumption. The results showed no significant association between the diversity ~~and~~ or abundance of the gut microbiota ~~with~~ and weight loss after TRF treatment for 12 weeks [31]. Those results differed from IF interventions (modified fasting with calorie restriction) in obese-metabolic syndrome individuals, in which ~~the~~ BMI and waist circumference were significantly reduced [39]. However, the latter also demonstrated that the link between gut microbiota composition and metabolic improvement depended on body weight change [39]. Several of the included studies [27, 34, 35, 39] indicate an independent association between the gut microbiota and many metabolism pathways, at least in relatively healthy individuals. On the other hand, changes in mealtime during Ramadan fasting could affect the human natural circadian rhythm, which might also have a detrimental effect on health, ~~which~~ and this needs further investigation to clarify.

This systematic review has both strengths and limitations. The strengths of our systematic reviews are ~~that~~ 1~~.~~) that ~~W~~we included human intervention studies that addressed the most frequent modalities of intermittent fasting accessible in the field~~;~~ and 2~~.~~) that we reported the change in diversity and composition of the gut microbiota in great detail. However, there are numerous limitations of this review~~.~~ , including 1~~.~~) ~~The~~ the small number of included studies from which we were able to extract data~~;~~ and 2~~.~~) ~~our~~ the broadness of our population eligibility criteria ~~were broad~~ (healthy, overweight/obese, and metabolic syndrome~~);~~). ~~t~~Therefore, the results could not be generalized. Another systematic study focusing on specific types of fasting and strict eligibility criteria (i.e., specific demographics) is warranted.

A meta-analysis would be ideal for this systematic review, but the variety of microbiota measures, particularly regional differences, could lead to difficulty. With this consideration, presumably, studies examining the effect of fasting on the gut microbiome could adhere to microbiome analysis best practices [63] and routinely report associations using standard alpha and beta diversity measurements. ~~The~~ ~~t~~Taxa investigations and reports should also be consistent.

Commented [SB19]: The intended meaning of this sentence was unclear. The phrase "is another type of IF" implied that the IF was different from the one in the first sentence, but the IF in that sentence appears to be described in parentheses as including TRF. It seems like what it might have referred to is the IF regimen. I also noted two studies using TRF, and one of them did not use the times listed in this sentence. I revised the text here to present the information as a report about the study of Gabel et al.

Conclusions

In conclusion, this systematic review suggests that IF modulates human gut microbiota diversity (both alpha and beta diversity). Human metabolic phenotype differences may alter alpha/beta diversity after a fasting intervention. Despite their variability, IF affects the gut microbiota at taxonomic levels in all metabolic phenotypes. Nevertheless, given the emerging recognition of the importance of intermittent fasting and the microbiome in physiological and pathological conditions, further investigations are warranted, ideally with adequately powered, long-term, placebo-controlled trials.

Acknowledgments

None.

Sources of Support

This work received no financial support for the research and publication of this article. Adriyan Pramono (A.P.) is supported for the junior scientist fellowship 2021 (RPI No. 185-67/UN7.6.1/PP/2021).

Commented [SB20]: This phrasing is unclear. I am unsure of the precise name of the fellowship, but here are some alternative phrasings that seem possible for the text here:

received support from a junior scientist fellowship in 2021
OR
was supported by a junior scientist fellowship in 2021
OR
received support from a 2021 junior scientist fellowship
OR
was supported by a 2021 junior scientist fellowship

Author contributions

A.P., M.A., E.K.S.L., E.R.N., and E.S.L. conceptualized the review. A.P. and M.A. wrote the protocol and performed the searching and data extraction. A.P., M.A., and E.K.S.L. performed the assessment of study quality ~~of study assessment~~. A.P. wrote the manuscript. M.A., E.K.S.L., E.R.N., E.S.L., and F.M.S. reviewed and revised the manuscript. All authors approved the final version of the manuscript.

Author Declarations

The authors declare no conflict of interest.

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Table 1. Characteristics of the fasting studies included in the~~e~~is systematic review on the effect of intermittent fasting on the gut microbiome

Table 2. Primary outcomes for gut microbiota diversity following fasting interventions

Table 3. ~~The e~~Effect of fasting on gut microbiota composition in humans

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